The Examiner states that the phrase "relevant disease or disorder" in Claim 11 renders the claim indefinite. Claim 11 has been amended to delete the phrase.

The Examiner states that the phrase "and/or" in Claims 12 and 17 renders the claims indefinite. Claims 12 and 17 have been amended to delete the phrase.

The Examiner states that the phrase "wherein the capsules and the prodrug are formulated in different forms" in Claim 16 renders the claim indefinite. Claim 16 has been amended to indicate that the capsules and the prodrug are formulated so that the capsules and the prodrug can be administered by different routes of administration.

The Examiner states that Claims 10 and 20 are indefinite since the claims do not set forth any steps involved in the claimed method/process. Claim 10 has been amended to recite steps for the claimed method, and Claim 20 has been amended to depend from Claim 10 and to further define the prodrug

The amendments to the claims referred to above, obviate the rejection 35 U.S.C. §112, second paragraph.

Rejection of Claims 10 and 20 under 35 U.S.C. §101

Claims 10 and 20 are rejected under 35 U.S.C. §101 "because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition pf a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 1201" (Office Action, page 3).

As indicated above, Claim 10 has been amended to recite steps for the claimed method in accordance with the Examiner's suggestion, and Claim 20 has been amended to depend from Claim 10 and to further define the prodrug.

Rejection of Claims 1-20 under 35 U.S.C. §112, first paragraph

Claims 1-20 are rejected under 35 U.S.C. §112, first paragraph "because the specification, while being enabling for a cellulose sulphate and polydimethyldiallylammonium capsule encapsulating cells transformed with a DNA sequence encoding cytochrome P450 operably linked to a promoter, wherein said cells express said DNA sequence, does not reasonably provide enablement for any capsule encapsulating any cytochrome P450 producing cells" (Office Action, page 4). The Examiner states that "[s]ince the material used to synthesize the capsule determines its structural and functional properties, predictability of which material

can be used to synthesize the capsule to produce the desired properties, requires a knowledge of how the encapsulation material relates to its functional properties" (Office Action, page 5). The Examiner further states that "[s]ince the cell used to synthesize cytochrome P450 determines the level of cytochrome P450 produced, predictability of which cells can be used to synthesize sufficient cytochrome P450 to affect tumors, requires a knowledge or teaching of how the level of expression of cytochrome P450 produced by the cell relates to the desired use" (Office Action, page 5). The Examiner concludes that:

> applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any capsule any cytochrome P450 producing cell... Without sufficient guidance, determination of those capsules comprising cytochrome P450 producing cells having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue (Office Action, pages 5-6).

Applicants respectfully disagree. With respect to the determination of enablement, it is not whether a particular method or technique entails some unpredictability; rather, the focus of the analysis is whether or not the particular method or technique requires undue experimentation. As amended, Applicants' claimed invention relates to a capsule encapsulating a cytochrome P450 expressing cell, said capsule comprising a polyelectrolyte complex and a porous membrane which allows prodrug molecules to pass into the capsule, wherein the prodrug molecules are converted into active drug molecules by cytochrome P450. The specification clearly provides sufficient guidance to enable those of skill in the art to make and use the claimed invention.

Citing the *Wands* case, the Examiner states that "Without sufficient guidance, determination of those capsules comprising cytochrome P450 producing cells having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue" (Office Action, page 6). Applicants agree with the Examiner that *Wands* is controlling precedent and encourage the Examiner to look to *Wands* as well for what it teaches about the application of the factors for assessing undue experimentation. *In re Wands*, 8 U.S.P.Q.2d. 1400, 1406 (Fed. Cir. 1988). That the outcome of an experiment (*e.g.*, an experiment designed to determine whether cytochrome P450 expressing cells and/or capsules other than those used by Applicants can be used in Applicants' claimed invention) is unpredictable does not mean that the experimentation is undue. Indeed, if an outcome is predictable, there would be no need to perform the experiment.

In *Wands*, the claims were rejected under 35 USC § 112, first paragraph by the Patent Office on the grounds that production of the claimed antibodies were unpredictable and unreliable, thus requiring undue experimentation. However, the court reversed the rejection stating that:

> In order to determine which anti-HBsAg antibodies satisfy all of the limitations of appellants' claims, the antibodies require <u>further screening</u> to select those which have an IgM isotype and have a binding affinity constant of at least $10^9 M^{-1}$ (*In re Wands*, 8 USPQ2d 1400, 1405 (Fed. Cir. 1988) (emphasis added).

As in the present case, the screening techniques needed to practice the *Wands* invention were well known in the art. Thus, the court further stated that:

> Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known (*Id.* at 1406).

Thus, the test is not simply quantitative. A considerable amount of experimentation is permissible if, as here, it is routine. As in the *Wands* case, Applicants have provided considerable direction and guidance. In the specification as filed, Applicants teach methods of isolating cytochrome P450; stable transfection of cells in order to obtain cells which express cytochrome P450; methods for determining whether the transfected cells express functional cytochrome P450; encapsulation of such cells in capsules comprising a polyelectrolyte complex and a porous membrane which allows prodrug molecules to pass into the capsule; methods of determining the viability and integrity of the capsules containing the cytochrome P450 expressing cells; and methods to assess whether the encapsulated cells can be used in combination with a prodrug which is activated by the cytochrome P450 to treat tumors *in vivo* (specification, Example 1). In addition, at the time of Applicants' invention, methods for transfecting cells to express a particular protein and determining whether such transfected cells synthesize sufficient levels of cytochrome P450 for use in the claimed invention were well known to those of skill in the art. Similarly, at the time of Applicants' invention several methods for encapsulating cells were well known to those of skill in the art (see, *e.g.*, Merten, O.W., *et al., Cytotechnology, 7:*121-130 (1991)). As was the case in *Wands*, upon consideration of the proper factors, no undue experimentation is involved. A considerable amount of experimentation is permissible if, as here, it is routine. Given the state of the art, the guidance in the specification, and detailed examples regarding how to prepare the claimed capsules and assess their function, it would not require undue experimentation to make and use the invention as claimed.

In view of the foregoing, it is respectfully submitted that Applicants have provided an enabling disclosure in compliance with 35 USC § 112, first paragraph.

Rejection of Claims 11-15 and 20 under 35 U.S.C. §112, first paragraph

Claims 11-15 and 20 are rejected under 35 U.S.C. §112, first paragraph, "because the specification, while being enabling for a method of decreasing a tumor comprising the direct insertion of the capsule into the tumor wherein expression of the DNA sequence results in an inhibition in tumor growth or a decrease in tumor size, does not reasonably provide enablement for a method of treating a cancer disease or any other relevant disease or disorder comprising administering to a subject in need thereof a therapeutically effective amount of the capsule of claim 1 and, either simultaneously or with a time span, a prodrug which is activated by cytochrome P450" (Office Action, page 6).

Claim 11 has been amended to recite a method of treating a tumor comprising administering to a subject in need thereof a therapeutically effective amount of the capsule according to Claim 1 and, either simultaneously or with a time span, a prodrug which is activated by cytochrome P450. Claim 20 has been amended to depend from Claim 10 and to further define the prodrug.

In view of the foregoing, it is respectfully submitted that Applicants have provided an enabling disclosure in compliance with 35 USC § 112, first paragraph.

Rejection of Claims 1-5 and 7-20 under 35 U.S.C. §102(a)

Claims 1-5 and 7-20 are rejected under 35 U.S.C. §102(a) "as being anticipated by Saller et al. (WO 97/01357)" (Office Action, page 8). The Examiner states that Saller *et al.* "teach the use of encapsulated cells producing viral particles for the treatment of tumors" and specifically, capsules formed from cellulose sulphate and polydimethyldiallyl-ammonium comprising a packaging cell containing a replication defective retroviral construct carrying the cytochrome P450 gene, pLX1256" (Office Action, page 9). The Examiner further states that Saller *et al.* "teach a pharmaceutical composition comprising said capsule and its use for the treatment of cancer. . . and "use of the above capsule in combination with a prodrug for the treatment of tumors" (Office Action, page 9).

Saller *et al.* teach encapsulated cells which produce viral particles, wherein the viral particles produced by the encapsulated cells are released from the capsule (Saller *et al.*, page 7,

Claim 1). Saller *et al.* also teach that the "viral particles produced by the encapsulated cells according to the invention, can be constructed to contain the genome of a viral vector carrying genes encoding marker and/or therapeutic genes", such as cytochrome P450 (Saller *et al.*, page 11). Thus, according to the teaching of Saller *et al.*, the viral particles pass from the capsules, the viral particles subsequently infect target host cells, and the genome of the viral vector, along with the gene encoding the marker/therapeutic gene present in the viral genome, is expressed within the infected host cell.

As amended, Applicants' claimed invention relates to a capsule encapsulating a cytochrome P450 expressing cell, said capsule comprising a polyelectrolyte complex and a porous membrane which allows prodrug molecules to pass into the capsule, wherein the prodrug molecules are converted into active drug molecules by cytochrome P450. Unlike Saller *et al.*, Applicants teach expression of the cytochrome P450 gene within the encapsulated cells which have been transduced with an expression vector comprising the cytochrome P450 gene. Cytochrome P450, which is a membrane-bound enzyme that functions when integrated into the membrane of cells, is not able to leave the transduced cells. Thus, the cytochrome P450 cannot pass out of or be delivered from Applicants' claimed capsule. According to Applicants' invention, the expressed cytochrome P450 protein integrates into the membrane of the encapsulated cells, and the encapsulated cells are injected or transplanted into or at the site of a tumor. A prodrug (*e.g.*, ifosfamide) is administered, wherein the prodrug enters the capsule and is converted into its active form by the cytochrome P450. Subsequently, the activated drug is delivered from the capsules and directly attacks the tumor.

Clearly, Saller *et al.* do not anticipate the subject matter of Applicants' claimed invention, particularly as amended.

Rejection of Claims 1, 8, 9 and 15-19 under 35 U.S.C. §103(a)

Claims 1, 8, 9 and 15-19 are rejected under 35 U.S.C. §103(a) as being unpatentable over Wei *et al.* in view of Tai *et al.* The Examiner states that Wei *et al.* teach that "malignant tumors of the central nervous system do not respond well to chemotherapy, specifically cyclophosphamide (CPA) because the conversion of CPA to DNA-alkylating cytotoxic metabolites is restricted to the liver"; that "cytochrome P450 2B1 activates the inert prodrug, Cpa into its cytotoxic metabolites" and that "the addition of cytochrome P450 2B1-producing fibroblasts followed by CPA administration, prevented meningeal neoplasia and led to partial

regression of parenchymal solid tumors in the brains of athymic mice, previously seeded with rat C6 gliomas" (Office Action, pages 9-10). The Examiner states that Tai *et al.* teach "an alternate strategy of gene therapy that involves immunoisolating genetically modified cells in a biocompatible membrane (a capsule), thereby introducing a system that can provide sustained delivery of the desired gene product to a tissue or group of cells" and use of "an alginate-poly-L-lysine semipermeable membrane that provided a microenvironment that was physiologically compatible with the growth of the modified cells and allowed easy diffusion of the secreted gene products without compromising the immunoisolating properties of the membrane" (Office Action, page 10). The Examiner states that:

> One of ordinary skill in the art at the time of filing would have been motivated to encapsulate the cytochrome P450 2B1-producing fibroblasts of Wei et al. in the capsule of Tai et al. such that said capsule comprises a porous membrane that allows cytochrome P450 to pass out of the capsule as well as the prodrug molecule, CPA, to pass into the capsule in order to supply cytochrome P450 activity to the prodrug, CPA, for its use as a chemotherapeutic agent. . . The ordinary artisan would have had a reasonable expectation of success at the time of filing based on the results of Wei et al. who showed that the addition by inoculation of cytochrome P450 2B1-producing fibroblasts to mice brains followed by CPA administration prevented meningeal neoplasia as well as the results of Tai et al. that showed significantly higher levels of human growth hormone from the recipients of encapsulated cells relative to the recipients of unencapsulated cells. . . Further the ordinary artisan would have been motivated at the time of filing to use the above capsule as part of a pharmaceutical composition or kit for the treatment of a cancer, because of the shown effectiveness of cytochrome P450 producing fibroblasts in helping to reduce tumor growth when administered in conjunction with the appropriate prodrug as taught by Wei et al. (Office Action, page 11).

Applicants respectfully disagree. Where the claimed invention is rejected as obvious in view of a combination of references, § 103 requires both (1) that "the prior art would have suggested to the person of ordinary skill in the art that they should . . . carry out the claimed process"; and (2) that the prior art should establish a reasonable expectation of success (*In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991)). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *Id.*

As amended, Applicants' claimed invention relates to a capsule encapsulating a cytochrome P450 expressing cell, said capsule comprising a polyelectrolyte complex and a porous membrane which allows prodrug molecules to pass into the capsule, wherein the prodrug molecules are converted into active drug molecules by cytochrome P450. As pointed out above,

Applicants teach expression of the cytochrome P450 gene within the encapsulated cells which have been transduced with an expression vector comprising the cytochrome P450 gene. Cytochrome P450, which is "an integral membrane protein" (Wei *et al.*, page 971, column 2) that functions when integrated into the membrane of cells, is not able to leave the transduced cells. Thus, the cytochrome P450 cannot be passed out of or be delivered from Applicants' claimed capsule. According to Applicants' invention, upon expression, the cytochrome P450 protein integrates into the membrane of the encapsulated cells, and the encapsulated cells are injected or transplanted into or at the site of a tumor. A prodrug (*e.g.*, ifosfamide) is administered, wherein the prodrug enters the capsule and is converted into its active form by the cytochrome P450. Subsequently, the activated drug is delivered from the capsules and directly attacks the tumor.

In contrast, Wei *et al.* teach a tumor therapy involving "introduction of the P450 2B1 gene into tumor cells" (Wei *et al.*, page 974, column 2). Wei *et al.* "demonstrate that C6 glioma cells, stably transfected with the P450 2B1 gene, become sensitive to CPA in culture" and that "intrathecal administration of P450 2B1-fibroblasts, followed by CPA, prevented meningeal neoplasia and led to partial regression of parenchymal solid tumors in the brains of athymic mice, previously seeded with rat C6 gliomas" (Wei *et al.*, page 969, column 2). Wei *et al.* do not teach or even suggest the use of a capsule encapsulating cytochrome P450 expressing cells to treat tumors.

Tai *et al.* transformed mouse fibroblasts with the human growth hormone gene (Ltk-GH) and encapsulated the transformed cells with an alginate-poly-L-lysine-alginate membrane. Tai *et al.* showed that "the encapsulation of the cells was physiologically compatible with growth and survival of the cells" (Tai *et al.*, page 1061, abstract). In addition, Tai *et al.* showed that "Balb-c mice transplanted with the encapsulated Ltk-GH cells had detectable serum levels of human growth hormone (hGH) for the duration of the study (115 days)" (Tai *et al.*, page 1061, abstract). In conclusion, Tai *et al.* state that "the studies presented here suggest that encapsulation of genetically modified fibroblasts may represent *a useful delivery system for recombinant proteins in vivo*" (Tai *et al.*, page 1068, column 1, emphasis added).

The combined teachings of Wei *e al.* and Tai *et al.* do not teach or even suggest encapsulating cells which express "an integral membrane protein" (Wei *et al.*, page 971, column 2) such as cytochrome P450, which integrates into the membrane of the cells expressing the protein, and thus, remains in the capsule. A person of skill in the art would not be motivated to combine the teachings of Wei *et al.* and Tai *et al.* for the purpose of encapsulating a cytochrome

P450 expressing cell, because cytochrome P450 would not "pass out" of capsules comprising such cells, and thus, would it would not be possible to introduce the cytochrome P450 into tumor cells as directed by Wei *et al.*. Furthermore, the cited art clearly does not teach or even suggest that a prodrug would enter the capsules comprising cells which express cytochrome P450, become converted to its active state by virtue of the cytochrome P450 protein integrated into the membrane of the encapsulated cells, and then pass through the porous capsules to function at the site of the tumor, and thus, cannot provide a reasonable expectation that this would occur successfully.

To solve the problem of providing a local, continuous and long-term conversion and delivery system of a drug, and thus, of a toxic substance, Applicants were faced with the following uncertainties:

1) Would cytochrome P450 expressing cells survive for a period of time within the capsules?

2) Would expression and integration of the enzyme into the membrane of the cells also work when the cells are encapsulated?

3) If so, would an integrated enzyme still work, that is, would the enzyme still convert the prodrug molecule into the drug molecule?

4) If so, would the drug molecules have a cytotoxic effect also on the encapsulated cells, and thus, prevent continuous conversion of the prodrug into the drug, and thus, prevent delivery of drug molecules to the tumor?

In Example 1 of the present invention Applicants show that "tumor reduction was most pronounced in mice that received encapsulated CY2B1 expressing cells by injection into the tumor and subsequent treatment with ifosfamide (Table 1)" (specification, page 29, 2nd paragraph). Thus, the finding that cytochrome P450 expressing cells survive for a period of time, that the enzyme is not only expressed but also integrated into the membrane and that the enzyme indeed converts prodrug molecules into drug molecules must be regarded as a surprising and unexpected result. Additionally, Applicants found that the drug produced within the capsules has a cytotoxic effect on the encapsulated cells (specification, pages 23-24, item 5), but that

nevertheless, continuous conversion of the prodrug into the drug is not prevented. Furthermore, it is reported by Shao *et al.*, a copy of which is being filed as the Exhibit, that encapsulation may, depending on the encapsulated cell type, cause problems, *inter alia*, that encapsulated cells can spread out of the capsules. However, as described on page 26 of the specification (item 7b), "no outgrowth of cells from these capsules was observed during the 6 week observation period, indicating that the capsules were still intact." The safety of the encapsulated cells was also demonstrated *in vivo* (specification, page 31, item 12). Further investigation showed that the capsules do not exhibit *in vivo* toxicity even in very sensitive organs. On page 27, item 8 of the specification, Applicants state that after application of the capsules to the pancreas, "[n]o pancreatitis could be observed on the morphological level nor did the animals express signs of illness."

Faced with the problems and uncertainties discussed above, the combined teachings of Wei *et al.* and Tai *et al.* do not motivate a person of skill in the art to use the method of Tai *et al.* to encapsulate cells expressing the integral membrane cytochrome P450 protein of Wei *et al.* for continuous long term conversion of a non-toxic prodrug into a cytotoxic drug and to implant such capsules *in vivo* into or at the site of a tumor for treatment thereof. Consequently, the combined teachings of Wei *et al.* and Tai *et al.* cannot provide a reasonable expectation in doing so.

Clearly, the combined teachings of Wei *et al.* and Tai *et al.* do not render obvious Applicants' claimed invention, particularly as amended.

Rejection of Claim 2 under 35 U.S.C. §103(a)

Claim 2 is rejected under 35 U.S.C. §103(a) as being unpatentable over Wei *et al.* and Tai *et al.* as applied above and further in view of Merten *et al.* The Examiner cites Merten *et al.* as teaching "a method for encapsulation of mammalian cells using capsules comprising cellulose sulphate and poly-dimethyl-diallyl-ammonium chloride (PDMDACC)" (Office Action, page 12). The Examiner states that "[o]ne of ordinary skill in the art would have been motivated at the time of filing, to encapsulate, as taught by Tai et al., the cytochrome P450 2B1-producing fibroblasts of Wei et al., in a capsule made of cellulose sulphate and poly-dimethyl-ammonium chloride as taught by Merten et al. because of advantages of encapsulating by this method compared to other methods due to the simplicity of the process" (Office Action, page 12).

As discussed above, the combined teachings of Wei *et al.* and Tai *et al.* do not render obvious Applicants' claimed invention. Merten *et al.* do not provide what is lacking in the combined teachings of the Wei *et al.* and Tai *et al.* references. Merten *et al.* developed an encapsulation system in which capsules "were produced using a solution of sodium cellulose phosphate (CS) (1.5%) and poly-dimethyl-diallyl-ammoniumchloride (PDMDAAC)" and tested the "influences of varying encapsulation process parameters on capsule characteristics, cell growth, and monoclonal antibody production" (Merten *et al.*, page 121, abstract). Merten *et al.* do not teach or even suggest encapsulattion of a cytochrome P450 expressing cell, the capsule comprising a polyelectrolyte complex and a porous membrane which allows prodrug molecules to pass into the capsule, wherein the prodrug molecules are converted into active drug molecules by cytochrome P450.

Clearly, the combined teachings of Wei *et al.* and Tai *et al.* in view of Merten *et al.* do not render obvious Applicants' claimed invention, particularly as amended.

Rejection of Claims 4, 5 and 7 under 35 U.S.C. §103(a)

Claims 4, 5 and 7 are rejected under 35 U.S.C. §103(a) as being unpatentable over Wei *et al.* and Tai *et al.* as applied above and further in view of Salmons *et al.* The Examiner cites Salmons *et al.* as teaching "the use of retroviral vectors (RV) for gene therapy and discuss the advantages and disadvantages of their use"; "the construction of retroviral vectors (RV) for targeted delivery and expression of therapeutic genes for gene therapies aimed at treating various cancers, inherited disorders and viral infections"; that "retroviral vectors are the vector of choice for gene transfer"; and the use of replication defective retroviruses (Office Action, pages 12-13). The Examiner states that:

> [o]ne of ordinary skill in the art would have been motivated at the time of filing, to encapsulate, as taught by Tai et al., a cytochrome P450 producing cell as taught by Wei et al. . . . wherein the cell is a packaging cell comprising a replication defective retroviral vector as taught by Salmons et al. carrying the cytochrome P450 gene in order to produce infective cytochrome P450 encoding retroviral vector capable of infecting a target tumor cell while the packaging cell remains immunoisolated. One of ordinary skill would have been motivated to place the above retroviral vector encoded cytochrome P450 gene under control of a target cell specific regulatory element or promoter so that the cytochrome P450 gene product would only be produced in the desired target cell, and not another cell where its production could be detrimental to the cell. . .One of ordinary skill would have had a reasonable expectation of success at the time of filing based on the results of Wei et al. who showed that the addition by inoculation of cytochrome P450 2B1-producing fibroblasts to mice brains followed by CPA

> administration prevented meningeal neoplasia as well as the results of Tai et al. that showed significantly higher levels of human growth hormone from the recipients of encapsulated cells relative to the recipients of unencapsulated cells as well as Salmons et al. who show successful results using the retroviral vector system for the expression of exogenous genes" (Office Action, page 14).

Applicants respectfully disagree. As amended, Claims 4, 5 and 7 relate to a capsule encapsulating a cytochrome P450 expressing cell and no longer refer to encapsulation of a packaging cell line.

As discussed above, the combined teachings of Wei *et al.* and Tai *et al.* do not render obvious Applicants' claimed invention. Salmons *et al.* do not provide what is lacking in the combined teachings of the Wei *et al.* and Tai *et al.* references. Salmons *et al.* discuss strategies that "should permit the construction of novel retroviral vectors that provide safe and targeted *in vivo* gene transfer" (Salmons *et al.*, page S53, abstract). Salmons *et al.* do not teach or even suggest encapsulattion of a cytochrome P450 expressing cell, the capsule comprising a polyelectrolyte complex and a porous membrane which allows prodrug molecules to pass into the capsule, wherein the prodrug molecules are converted into active drug molecules by cytochrome P450.

Clearly, the combined teachings of Wei *et al.* and Tai *et al.* in view of Salmons *et al.* do not render obvious Applicants' claimed invention, particularly as amended.

Rejection of Claim 6 under 35 U.S.C. §103(a)

Claim 6 is rejected under 35 U.S.C. §103(a) as being unpatentable over Wei *et al.*, Tai *et al.* and Salmons *et al.* as above and further in view of Gunzburg *et al.* The Examiner states that Gunzburg *et al.* "teach a retroviral vector useful as a gene transfer vehicle for targeted gene therapy", and specifically, a retroviral vector comprising a 5' LTR region of the structure U3-R-U5; one or more sequences selected from coding and non-coding sequences; and a 3' LTR region comprising a completely or partially deleted U3 region wherein said deleted U3 region is replaced by a polylinker sequence, followed by the R and U5 region" (Office Action, page 15). The Examiner states that:

> one of ordinary skill in the art would have been motivated at the time of filing, to encapsulate, as taught by Tai et al., a cytochrome P450 producing cell as taught by Wei et al. and discussed above, wherein the cell is a packaging cell comprising a replication defective retroviral vector as taught by Salmons et al. carrying the cytochrome P450 gene in order to produce infective cytochrome P450 encoding retroviral vector capable of infecting a target tumor cell while the packaging cell

> remains immunoisolated. One of ordinary skill in the art would have been further motivated at the time of filing to use the retroviral vector taught by Gunzburg et al. that encodes cytochrome P450 gene as the transfer vehicle because of its reduced probability to undergo recombination with the packaging construct, thus resulting in prolonged production of cytochrome P450 encoding retroviral vector (Office Action, page 15).

Applicants respectfully disagree. As amended Claim 6 relates to a capsule encapsulating a cytochrome P450 expressing cell and no longer refers to encapsulation of a packaging cell line.

The combined teachings of Wei *et al.*, Tai *et al.* and Salmons *et al.* have been discussed above. Gunzburg *et al.* do not provide what is lacking in the combined teachings of the Wei *et al.*, Tai *et al.* and Salmons *et al.* references. Gunzburg *et al.* teach a particular retroviral vector "which undergoes promoter conversion comprising a 5'LTR region of the structure U3-R-U5; one or more sequences selected from coding and non-coding sequences; and a 3' LTR region comprising a completely or partially deleted U3 region wherein the deleted U3 region is replaced by a polylinker sequence, followed by the R and U5 region" (Gunzburg *et al.*, Claim 1). Gunzburg *et al.* do not teach or even suggest encapsulattion of a cytochrome P450 expressing cell, the capsule comprising a polyelectrolyte complex and a porous membrane which allows prodrug molecules to pass into the capsule, wherein the prodrug molecules are converted into active drug molecules by cytochrome P450.

Clearly, the combined teachings of Wei *et al.*,Tai *et al.* and Salmons *et al.* in view of Gunzburg *et al.* do not render obvious Applicants' claimed invention, particularly as amended.

Provisional Rejection of Claims 1-20 under the judicially created doctrine of obviousness-type double patenting

Claims 1-20 "are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13 and 15 of copending Application No. 08/996,460" (Office Action, page 16). The Examiner states that [a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because they claim common subject matter" (Office Action, page 16).

As amended, Applicants' claimed invention relates to a capsule encapsulating a cytochrome P450 expressing cell, said capsule comprising a polyelectrolyte complex and a porous membrane which allows prodrug molecules to pass into the capsule, wherein the prodrug molecules are converted into active drug molecules by cytochrome P450. Unlike Saller *et al.*,

Applicants teach expression of the cytochrome P450 gene within the encapsulated cells which have been transduced with an expression vector comprising the cytochrome P450 gene. Cytochrome P450, which is a membrane-bound enzyme that functions when integrated into the membrane of cells, is not able to leave the transduced cells. Thus, the cytochrome P450 cannot be delivered from Applicants' claimed capsule. According to Applicants' invention, the expressed cytochrome P450 protein integrates into the membrane of the encapsulated cells, and the encapsulated cells are injected or transplanted into or at the site of a tumor. A prodrug (*e.g.*, ifosfamide) is administered, wherein the prodrug enters the capsule and is converted into its active form by the cytochrome P450. Subsequently, the activated drug is delivered from the capsules and directly attacks the tumor.

Application No. 08/996,460 (referred to as Saller *et al.*) is a continuation application of PCT/EP96/02748 (WO 97/01357) which is cited above in support of a novelty rejection herein. As discussed above, Saller *et al.* teach encapsulated cells which produce viral particles, wherein the viral particles produced by the encapsulated cells are released from the capsule (Saller *et al.*, page 9, Claim 1). Saller *et al.* also teach that the "viral particles produced by the encapsulated cells according to the invention, can be constructed to contain the genome of a viral vector carrying genes encoding marker and/or therapeutic genes", such as cytochrome P450 (Saller *et al.*, page 14). Thus, according to the teaching of Saller *et al.*, the viral particles are released from the capsules, the viral particles subsequently infect target host cells, and the genome of the viral vector, along with the gene encoding the marker/therapeutic gene present in the viral genome, is expressed within the infected host cell. Saller *et al.* do not teach or even suggest encapsulattion of a cytochrome P450 expressing cell, the capsule comprising a polyelectrolyte complex and a porous membrane which allows prodrug molecules to pass into the capsule, wherein the prodrug molecules are converted into active drug molecules by cytochrome P450.

Clearly, Saller *et al.* do not render obvious the subject matter of Applicants' claimed invention, particularly as amended.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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